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CHAPTER 89

Oral Solid Dosage Forms

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Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules. Large-scale production methods used for their preparation, as described later in the chapter, require the presence of other materials in addition to the active ingredients. Additives also may be included in the formulations to enhance the physical appearance, improve stability and aid in disintegration after administration. These supposedly inert ingredients, as well as the production methods employed, have been shown in some cases to influence the release of the drug substances.¹ Therefore care must be taken in the selection and evaluation of additives and preparation methods to ensure that the physiological availability and therapeutic efficacy of the active ingredient will not be diminished.

In a limited number of cases it has been shown that the drug substance's solubility and other physical characteristics have influenced its physiological availability from a solid dosage form. These characteristics include its particle size, whether it is amorphous or crystalline, whether it is solvated or nonsolvated and its polymorphic form. After clinically effective formulations are obtained, variations among dosage units of a given batch, as well as batch-to-batch differences, are reduced to a minimum through proper in-process controls and good manufacturing practices. The recognition of the importance of validation both for equipment and processes has greatly enhanced assurance in the reproducibility of formulations. It is in these areas that significant progress has been made with the realization that large-scale production of a satisfactory tablet or capsule depends not only on the availability of a clinically effective formulation

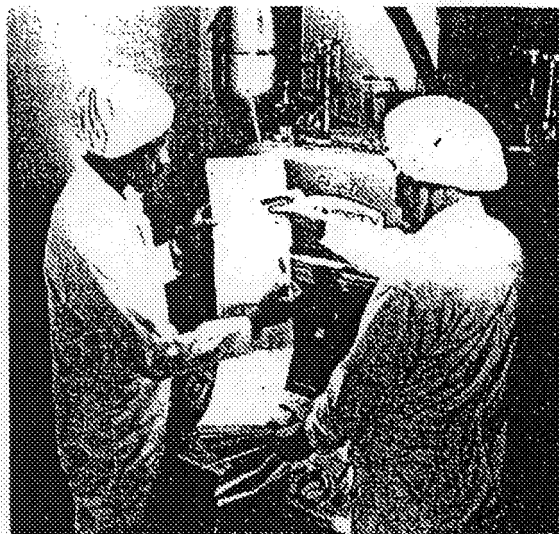


Fig 89-1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly).

but also on the raw materials, facilities, personnel, validated processes and equipment, packaging and the controls used during and after preparation (Fig 89-1).

Tablets

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. The term *compressed tablet* is believed to have been used first by John Wyeth and Brother of Philadelphia. During this same period, molded tablets were introduced to be used as "hypodermic" tablets for the extemporaneous preparation of solutions for injection. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste and ease of administration).

Although the basic mechanical approach for their manufacture has remained the same, tablet technology has undergone great improvement. Efforts are being made continually to understand more clearly the physical characteristics of tablet compression and the factors affecting the availability

of the drug substance from the dosage form after oral administration. Compression equipment continues to improve both as to production speed and the uniformity of tablets compressed. Recent advances in tablet technology have been reviewed.⁸⁻¹³

Although tablets frequently are more discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. They are divided into two general classes, whether they are made by compression or molding. Compressed tablets usually are prepared by large-scale production methods while molded tablets generally involve small-scale operations. The various tablet types and abbreviations used in referring to them are listed below.

Compressed Tablets (CT)

These tablets are formed by compression and contain no special coating. They are made from powdered, crystalline or granular materials, alone or in combination with binders, disintegrants, lubricants, diluents and in many cases, colorants.

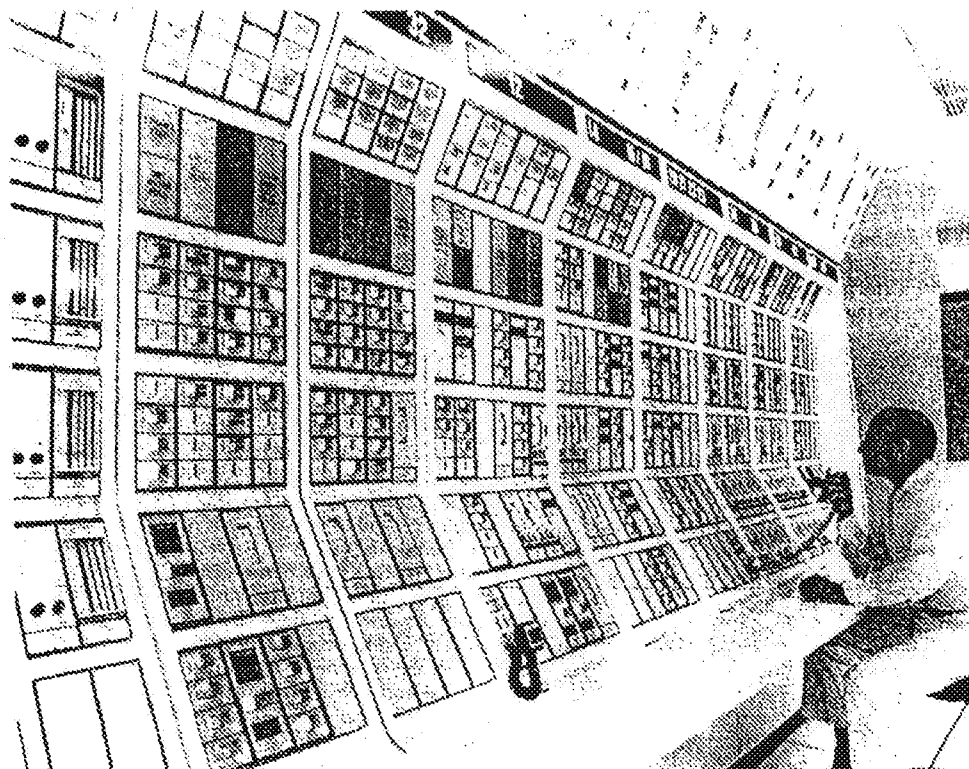


Fig 89-11. Computer control room for the first large-scale computer-controlled tablet manufacturing facility (courtesy, MSD).

prolonged dissolution rate. Compaction mills available include the Chilsonator (*Fitzpatrick*), Roller Compactor (*Vector*) and the Compactor Mill (*Allis-Chalmers*).

Direct Compression

As its name implies, direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. Formerly, direct compression as a method of tablet manufacture was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals such as potassium salts (chlorate, chloride, bromide, iodide, nitrate, permanganate), ammonium chloride and methenamine. These materials possess cohesive and flow properties which make direct compression possible.

Since the pharmaceutical industry constantly is making efforts to increase the efficiency of tableting operations and reduce costs by using the smallest amount of floor space and labor as possible for a given operation, increasing attention is being given to this method of tablet preparation. Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of imparting the characteristics required for compression, and the use of force-feeding devices to improve the flow of powder blends.

For tablets in which the drug itself constitutes a major portion of the total tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed directly. Direct compression for tablets containing 25% or less of drug substances frequently can be used by formulating with a suitable diluent which acts as a carrier or vehicle for the drug.²⁷⁻²⁹

Direct-compression vehicles or carriers must have good

flow and compressible characteristics. These properties are imparted to them by a preprocessing step such as wet granulation, slugging, spray drying, spheronization or crystallization. These vehicles include processed forms of most of the common diluents including dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol and microcrystalline cellulose. These commercially available direct-compression vehicles may contain small quantities of other ingredients (eg, starch) as processing aids. Dicalcium phosphate dihydrate (*Di-Tab*, *Stauffer*) in its unmilled form has good flow properties and compressibility. It is a white crystalline agglomerate insoluble in water and alcohol. The chemical is odorless, tasteless and nonhygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation.

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness. One commercial source is *Di-Pac* (*Amarstar*) prepared by the cocrystallization of 97% sucrose and 3% dextrins. Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrated lactose does not flow and its use is limited to tablet formulations prepared by the wet granulation method. Both anhydrous lactose and spray-dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present. Mannitol is a popular diluent for chewable tablets due to its pleasant taste and mouthfeel resulting from its negative heat of solution. In its

granular form (*ICI Americas*) it has good flow and compressible qualities. It has a low moisture content and is not hygroscopic.

The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (*Avicel, FMC*). This nonfibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades which range in average particle size from 20 μm to 100 μm . It is water-insoluble but the material has the ability to draw fluid into a tablet by capillary action; it swells on contact and thus acts as a disintegrating agent. The material flows well and has a degree of self-lubricating qualities, thus requiring a lower level of lubricant as compared to other excipients.

Forced-flow feeders are mechanical devices available from pharmaceutical equipment manufacturers designed to de-aerate light and bulky material. Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure. By increasing the density of the powder, higher uniformity in tablet weights is obtained. See Fig 89-25.

Recently, many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as "forgiving" as were the older wet-granulated products. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations. Interest in direct compression also is stimulating basic research on the flowability of powders with and without the presence of additives. Direct compression formulas are included in the formula section found on page 1654.

Related Granulation Processes

Spheronization—Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations. Since the particles are round, they have good flow properties when dried. They can be formulated to contain sufficient binder to impart cohesiveness for tableting. Spheronization equipment such as the Marumerizer (*Luwa*) and the CF-Granulator (*Vector*) is commercially available. A wet granulation containing the drug substance, diluent (if required) and binder, is passed first through an extruding machine to form rod-shaped cylindrical segments ranging in diameter from 0.5 to 12 mm. The segment diameter and the size of the final spherical particle depend on the extruder screen size. After extrusion the segments are placed into the Marumerizer where they are shaped into spheres by centrifugal and frictional forces on a rotating plate (see Fig 89-12). The pellets then are dried by conventional methods, mixed with suitable lubricants and compressed into tablets, or used as capsule-fill material. Micro-

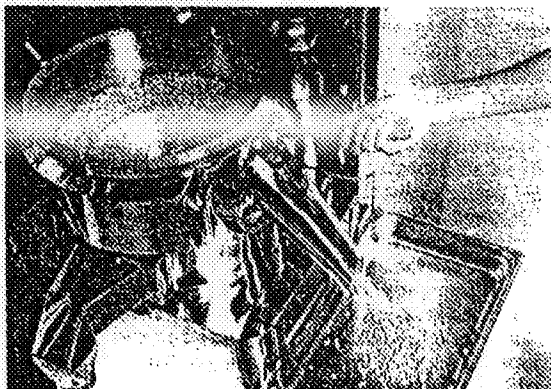


Fig 89-12. The inside of a QJ-400 Marumerizer (courtesy, Luwa).

crystalline cellulose has been shown to be an effective diluent and binder in granulations to be spheronized.³⁰⁻³³ The

dry process allows the production of granules, regular in shape, size and surface characteristics; low friability resulting in fewer fines and dust; and the ability to regulate the size of the spheres within a narrow particle-size distribution.

Spheres also can be produced by fluid-bed granulation techniques and by other specialized equipment such as the CF-Granulator (*Vector*). These processes, however, must begin with crystals or nonpareil seeds followed by buildup. Exact results, such as sphere density, are different for the various methods and could be important in product performance. These processes can be run as batches or continuously.

Spray-Drying—A number of tableting additives suitable for direct compression have been prepared by the drying process known as spray-drying. The method consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The feed liquid may be a solution, slurry, emulsion, gel or paste, provided it is pumpable and capable of being atomized. As shown in Fig 89-13, the feed is sprayed into a current of warm filtered air. The air supplies the heat for evaporation and conveys the dried product to the collector; the air is then exhausted with the moisture. As the liquid droplets present a large surface area to the warm air, local heat and transfer coefficients are high.

The spray-dried powder particles are homogeneous, approximately spherical in shape, nearly uniform in size and frequently hollow. The latter characteristic results in low bulk density with a rapid rate of solution. Being uniform in size and spherical, the particles possess good flowability. The design and operation of the spray-dryer can vary many characteristics of the final product, such as particle size and size distribution, bulk and particle densities, porosity, moisture content, flowability and friability. Among the spray-dried materials available for direct compression formulas are lactose, mannitol and flour. Another application of the process in tableting is spray-drying the combination of tablet additives as the diluent, disintegrant and binder. The spray-dried material then is blended with the active ingredient or drug, lubricated and compressed directly into tablets.

Since atomization of the feed results in a high surface area, the moisture evaporates rapidly. The evaporation keeps the product cool and as a result the method is applicable for drying heat-sensitive materials. Among heat-sensitive pharmaceuticals successfully spray-dried are the amino acids; antibiotics as aureomycin, bacitracin, penicillin and streptomycin; ascorbic acid; cascara extracts; liver extracts; pepsin and similar enzymes; protein hydrolysates and thiamine.³⁴

Frequently, spray-drying is more economical than other processes since it produces a dry powder directly from a liquid and eliminates other processing steps as crystallization, precipitation, filtering or drying, particle-size reduction and particle classifying. By the elimination of these

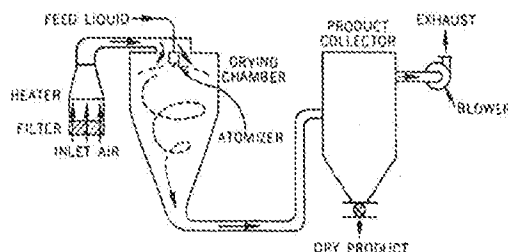


Fig 89-13. Typical spray-drying system (courtesy, Bowen Eng).

Fluid-Bed Granulation Method**CT Ascorbic Acid USP, 50 mg**

Ingredients	In each	In 10,000
Ascorbic Acid USP (powder no 80)*	55 mg	550 g
Lactose	21 mg	210 g
Starch (potato)	13 mg	130 g
Ethylcellulose N100 (80-105 cps)	16 mg	160 g
Starch (potato)	7 mg	70 g
Talc	6.5 mg	65 g
Calcium stearate	1 mg	10 g
Weight of granulation		1195.0 g

* Includes 10% in excess of claim

Add the first three ingredients to the granulator. Mix for 5 to 15 min or until well-mixed. Dissolve the ethylcellulose in anhydrous ethanol and spray this solution, and any additional ethanol, into the fluidized mixture. Cease spraying when good granules are produced. Dry to approximately 3% moisture. Remove the granules and place them in a suitable blender. Sequentially add the remaining three ingredients with mixing steps in between each addition. Compress using a flat, beveled, 1/4-in punch. 20 tablets should weigh 2.39 g.

Sustained-Release (SR) procainamide tablets

Ingredients	In each	In 10,000
Procainamide	500 mg	5,000 g
HPMC 2208, USP	300 mg	3,000 g
Carnauba wax	60 mg	600 g
HPMC 2910, USP	30 mg	300 g
Magnesium stearate	4 mg	40 g
Stearic acid	11 mg	110 g
Talc	5 mg	50 g
Weight of granulation		9,100 g

Place the first three ingredients in the granulator and mix for 5 to 15 min. Dissolve the HPMC in water (mix in hot water, then cool down) and spray into the fluidized mixture. Dry to approximately 5% moisture. Sequentially add the last three ingredients with mixing steps in between each addition. Compress, using capsule-shaped tooling. 10 tablets should weigh 9.1 g.

Dry Granulation Method**CT Acetylsalicylic Acid**

Ingredients	In each	In 7000
Acetylsalicylic Acid (crystals 20-mesh)	0.325 g	2275 g
Starch		226.8 g
Weight of granulation		2501.8 g

Dry the starch to a moisture content of 10%. Thoroughly mix this with the acetylsalicylic acid. Compress into slugs. Grind the slugs to 14- to 16-mesh size. Recompress into tablets, using a 13/32-in punch. 10 tablets should weigh 3.575 g.

CT Sodium Phenobarbital

Ingredients	In each	In 7000
Phenobarbital sodium	65 mg	455 g
Lactose (granular, 12-mesh)	26 mg	182 g
Starch	20 mg	140 g
Talc	20 mg	140 g
Magnesium stearate	0.3 mg	2.1 g
Weight of granulation		919.1 g

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a 1/2-in concave punch. 10 tablets should weigh 1.3 g.

CT Vitamin B Complex

Ingredients	In each	In 10,000
Thiamine mononitrate ^a	0.733 mg	7.33 g
Riboflavin ^a	0.733 mg	7.33 g
Pyridoxine hydrochloride	0.333 mg	3.33 g
Calcium pantothenate ^a	0.4 mg	4 g
Nicotinamide	5 mg	50 g
Lactose (powder)	75.2 mg	752 g
Starch	21.9 mg	219 g
Talc	20 mg	200 g
Stearic acid (powder)	0.701 mg	7.01 g
Weight of granulation		1259 g

^a Includes 10% in excess of claim.

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a 1/4-in concave punch. 10 tablets should weigh 1.25 g.

Sufficient tartaric acid should be used in these tablets to adjust the pH to 4.5.

Direct Compression Method**APC Tablets**

Ingredients	In each	In 10,000
Aspirin (40-mesh crystal)	224 mg	2240 g
Phenacetin	160 mg	1600 g
Caffeine (Anhyd USP gran)	32 mg	320 g
Compressible sugar (Di-Pac ^a)	93.4 mg	934 g
Sterotex	7.8 mg	78 g
Silica gel (Syloid 244 ^b)	2.8 mg	28 g

^a Amstar.^b Davison Chem.

Blend ingredients in twin-shell blender for 15 minutes and compress on 13/32-in standard concave punch (courtesy, Amstar).

CT Ascorbic Acid USP, 250 mg

Ingredients	In each	In 10,000
Ascorbic Acid USP (Merck, fine crystals)	255 mg	2550 g
Microcrystalline cellulose ^a	159 gm	1590 g
Stearic acid	9 mg	90 g
Colloidal silica ^b	2 mg	20 g
Weight of granulation		4250 g

^a Avicel-PH-101.^b Cab-O-Sil.

Blend all ingredients in a suitable blender. Compress, using 7/8-in standard concave punch. 10 tablets should weigh 4.25 g (courtesy, FMC).

Breath Freshener Tablets

Ingredients	In each	In 10,000
Wintergreen oil	0.6 mg	6 g
Menthol	0.85 mg	8.5 g
Peppermint oil	0.3 mg	3 g
Silica gel (Syloid 244 ^a)	1 mg	10 g
Sodium saccharin	0.3 mg	3 g
Sodium bicarbonate	14 mg	140 g
Mannitol USP (granular)	180.95 mg	1809.5 g
Calcium stearate	2 mg	20 g

^a Davison Chem.